Overview

A Review of the Clinical Evidence for Intensity-modulated Radiotherapy

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Abstract

Aims: Intensity-modulated radiotherapy (IMRT) is a development of three-dimensional conformal radiotherapy that offers improvements in dosimetry in many clinical scenarios. Here we review the clinical evidence for IMRT and present ongoing or unpublished randomised controlled trials (RCTs).
Methods: We identified randomised and non-randomised comparative studies of IMRT and conventional radiotherapy using MEDLINE, hand-searching *Radiotherapy and Oncology* and the *International Journal of Radiation Oncology, Biology and Physics* and the proceedings of the American Society for Therapeutic Radiology and Oncology and the European Society for Therapeutic Radiology and Oncology annual meetings. The *meta*Register of Controlled Trials was searched to identify completed-unpublished, ongoing and planned RCTs.
Results: Sixty-one studies comparing IMRT and conventional radiotherapy were identified. These included three RCTs in head and neck cancer (205 patients) and three in breast cancer (664 patients) that had reported clinical outcomes; these were all powered for toxicity-related end points, which were significantly better with IMRT in each trial. There were 27 additional non-randomised studies in head and neck (1119 patients), 26 in prostate cancer (>5000 patients), four in breast cancer (875 patients) and nine in other tumour sites. The results of these studies supported those of the RCTs with benefits reported in acute and late toxicity, health-related quality of life and tumour control end points. Twenty-eight completed-unpublished, ongoing or planned RCTs incorporating IMRT were identified, including at least 12,310 patients, of which 15 compared conventional radiotherapy within IMRT as a randomisation or pre-planned stratification.
Discussion: Inverse-planned IMRT maintains parotid saliva production and reduces acute and late xerostomia during radiotherapy for locally advanced head and neck cancer, reduces late rectal toxicity in prostate cancer patients allowing safe dose escalation and seems to reduce toxicity in several other tumour sites. Forward-planned IMRT reduces acute toxicity and improves late clinician-assessed cosmesis compared with conventional tangential breast radiotherapy.
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Key words: Comparative study; evidence; IMRT; intensity-modulated radiotherapy; randomised clinical trial

Statement of Search Strategies Used and Sources of Information

There has been one systematic review by Veldeman *et al.* [1] of comparative clinical studies of intensity-modulated radiotherapy, in which MEDLINE and EMBASE were searched for publications up to 21 August 2007. No publications were found only using EMBASE. This study has updated that review with MEDLINE using technique-specific terms up to 21 July 2009. In addition, all issues of *Radiotherapy and Oncology* and the *International Journal of Radiation Oncology, Biology and Physics* between these dates, including the proceedings of the 2007 and 2008 American Society for Therapeutic Radiology and Oncology and European Society for Therapeutic Radiology and Oncology annual meetings, were hand-searched. Finally, the results of PARSPORT: ICRCTN48243537, which were presented at the American Society of Clinical Oncology annual meeting in 2009, as this

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paper was being reviewed, have been included. The *meta*-Register of Controlled Trials was searched using technique-specific terms up to 21 July 2009 to identify randomised controlled trials comparing intensity-modulated radiotherapy and conventional radiotherapy and trials that were stratified for use of intensity-modulated radiotherapy.

Introduction

The Radiotherapy Development Board was set-up as a multi-institutional body to implement the recommendations of the National Radiotherapy Advisory Group report to Ministers [2]. As discussed in the introduction of this special issue [3], the Radiotherapy Development Board identified the implementation of intensity-modulated radiotherapy (IMRT) and equitable access to IMRT across the four countries of the UK as its initial priority. We felt that an updated review of the clinical evidence to support the use of IMRT was essential and that such a review would help oncologists achieve a clinical consensus on the role of IMRT, a process considered essential for a successful introduction of a national IMRT programme by the Cancer Care Ontario Program [4].

IMRT offers improved dosimetry compared with conventional non-modulated radiotherapy techniques, including two-dimensional radiotherapy (2DRT) and three-dimensional conformal radiotherapy (3DCRT) in many clinical scenarios. IMRT can create concave dose distribution and steep dose gradients, sparing normal tissue; it can also be used to improve the homogeneity of the dose distribution. There is a potential for increased geographical miss as an IMRT dose distribution is more conformal than 3DCRT and delivery times can be longer [5]; four-dimensional adaptive image-guided radiotherapy (4D-IGRT) may provide solutions in the long term, but this is not routinely available within the UK [2]. IMRT results in larger volumes of normal tissues receiving low doses of radiation compared with conventional treatment, but the clinical relevance of this is unknown [6,7]. IMRT is a complex treatment to deliver and requires additional resources for education, outlining, planning and process quality assurance [8].

A systematic review of comparative studies was published in April 2008; 41 studies, including three randomised controlled trials (RCTs), were identified in a search up to 21 August 2007 [1]. This overview will update that review, prioritising data from prospective clinical trials, and summarise unpublished trials that are registered on the *meta*Register of Controlled Trials. Dosimetric planning studies, including comparisons of different IMRT planning and delivery techniques, are beyond the scope of this paper. This paper represents the views of the authors, and has not been formally approved by all of the organisations represented.

Materials and Methods

Search Strategy

There has been one systematic review by Veldeman *et al.* [1] of comparative clinical studies of IMRT, in which MEDLINE

and EMBASE were searched for publications up to 21 August 2007. No publications were found only using EMBASE [9]. This overview has updated that review with MEDLINE using technique-specific terms up to 21 July 2009. In addition, all issues of *Radiotherapy and Oncology* and the *International Journal of Radiation Oncology, Biology and Physics* between these dates, including the proceedings of the 2007 and 2008 American Society for Therapeutic Radiology and Oncology and European Society for Therapeutic Radiology and Oncology annual meetings, were hand-searched. Finally, the results of PARSPORT: ICRCTN48243537, which were presented at the American Society of Clinical Oncology annual meeting in 2009, as this paper was being reviewed, have been included [10]. The *meta*Register of Controlled Trials was searched using technique-specific terms up to 21 July 2009 to identify RCTs comparing IMRT and conventional radiotherapy and trials that were stratified for use of IMRT [11].

Definitions of Terms

The terms used in this review are taken from the International Atomic Energy Agency *Transition from 2D radiotherapy to 3D conformal and intensity-modulated radiotherapy*' document [11]. In this document, IMRT is described as 'more than simply the use of non-uniform beam intensities' and 'more than the use of beam modifiers such as wedges and compensators'. 'IMRT requires a treatment planning system (TPS) that allows 3D target volume and organ at risk delineation, defined dose plan objectives, formal plan assessment using 3D dose distribution and DVH criteria (as a minimum) and enhanced patient specific quality assurance'. A key aspect of 'inverse-planned' IMRT is plan optimisation, although the method of optimisation is achieved differently with each planning system. The basic principle is the setting of target coverage and normal tissue avoidance objectives that the TPS attempts to achieve with different beam intensities from each gantry angle. Each attempt is 'costed', with cycles of attempts or 'iterations', until an optimal balance between target coverage and normal tissue avoidance is reached. Human interaction is then needed to assess plan quality and if the optimised solution is unacceptable, changes are made to the initial plan objectives and the optimisation process re-run.

Forward-planned IMRT is a term used to describe the creation of complex two- or three-dimensional treatment plans by planners as opposed to the TPS. It creates less complex IMRT solutions than inverse-planned IMRT, generally to a maximum of three intensity levels per beam, but does not require the complex process quality assurance, and is thus a more direct extension of 3DCRT than inverse-planned IMRT. It is also not a new technique, being used primarily to deliver concomitant boosts and improve dosimetric homogeneity [12–16]. The additional dosimetric benefit of inverse-planned IMRT over forward-planned IMRT, if any, will depend on the clinical scenario [17–19]. Here, IMRT refers to inverse-planned IMRT except for tangential breast radiotherapy, as forward-planned IMRT is clearly distinct from conventional techniques, as described below. There are several techniques described for achieving forward-planned

tangential breast IMRT plans and they do not all require target volume and organ at risk delineation or assessment of the three-dimensional dose distribution; the principle is a three-dimensional assessment of breast thickness or dose and the use of filler beams to reduce the volume of tissue receiving <95% or >105% of the prescribed dose [19–21].

Results

In total, 61 comparative studies were identified, of these six were RCTs. One of these had only been published as an abstract and one only reported dosimetric results (the Veldeman *et al.* review [1] included three RCTs and a total of 49 studies). The details of these studies are presented by tumour site below. Twenty-seven additional unpublished, ongoing or planned trials in nine cancer sites were identified (Tables 1–4) and at least 12 310 patients have been or will be recruited to trials involving IMRT (eight trials do not state their planned trial numbers).

Head and Neck Cancer (30 Studies, Three Randomised Controlled Trials)

Radiotherapy is used in the radical management of patients with head and neck cancer in many different clinical scenarios. It is used as a single agent or in combination with surgery, chemotherapy or molecularly targeted agents. Target structures include the primary, involved and uninvolved lymph nodes.

Several critical structures limit tumour dose, including the parotid glands, spinal cord, optic apparatus and the swallowing apparatus. Late toxicity has focussed on xerostomia and there is a well-documented relationship between the volume of parotid gland irradiated to 25–30 Gy and the long-term recovery of salivary function [22,23]. IMRT has primarily been used to reduce parotid gland irradiation, minimising volumes receiving 26 Gy, although improved tumour coverage, reduced inhomogeneity and dose escalation have also been reported. Concerns over geographical miss and unexpected patterns of failure are now being reported [24,25]. Reduced toxicity from IMRT may allow dose escalation or incorporation of concurrent systemic therapies, both of which might improve outcome [26]. Biological imaging may alter concepts in target delineation by identifying sites of increased clonogenic density or relative radioresistance [27], to which IMRT could be used to deliver concomitant boosts [28].

Thirty studies comparing the results of IMRT with conventional radiotherapy for head and neck cancers were identified. These included two RCTs in nasopharyngeal cancer patients treated in China (total 111 patients), one RCT

Table 1
Ongoing, unreported and planned clinical trials in intensity-modulated radiotherapy (IMRT) in other head and neck cancers.

Study name	Principle research question	Number of patients	Status	Trial sponsor	Code
Study of three-dimensional conformal radiotherapy vs intensity-modulated radiotherapy for squamous cell carcinoma of the head and neck	Phase II RCT of 3DCRT versus IMRT	60	Active not recruiting	Tata Memorial Hospital, India	NCT 00652613
A multicentre randomised study of cochlear sparing intensity-modulated radiotherapy versus conventional radiotherapy in patients with parotid tumours (COSTAR)	Phase III RCT of 3DCRT versus IMRT	84	Recruiting	Institute of Cancer Research, UK	ISRCTN 81772291
IMRT plus cisplatin versus conventional radiotherapy plus cisplatin in stage III–IV HNSCC	Phase III RCT of dose-escalated IMRT versus standard dose 3DCRT	Not stated	Recruiting	Group Oncologie Radiotherapie, France	NCT 00158678
Radiation therapy and cisplatin with or without cetuximab in treating patients with stage III or stage IV head and neck cancer	Phase III RCT of concurrent accelerated chemoradiation with or without cetuximab, stratified for use of IMRT	720	Recruiting	RTOG; NCI, USA	NCT 00265941
A phase III study of standard fractionation radiotherapy with concurrent high-dose cisplatin versus accelerated fractionation radiotherapy with panitumumab in patients with locally advanced stage III and IV squamous cell carcinoma of the head and neck	Phase III RCT of standardly fractionated chemoradiation versus accelerated panitumumab–radiotherapy, stratified for use of IMRT	Not stated	Recruiting	Princess Margaret Hospital; NCIC, Canada	NCT 00820248
Late-course accelerated hyperfractionated IMRT for locoregionally advanced nasopharyngeal carcinoma	Phase II/III RCT of conventionally fractionated versus late-course accelerated hyperfractionated IMRT	Not stated	Recruiting	Guangxi Medical University, China	NCT 00778908

RCT, randomised controlled trial; 3DCRT, three-dimensional conformal radiotherapy; RTOG, Radiation Therapy Oncology Group; NCI, National Cancer Institute; NCIC, National Cancer Institute of Canada.

Table 2
Ongoing, unreported and planned clinical trials in intensity-modulated radiotherapy (IMRT) in prostate cancer.

Study name	Principle research question	Number of patients	Status	Trial sponsor	Code
A phase III intensity-modulated radiotherapy dose-escalation trial for prostate cancer using hypofractionation	Phase III RCT of standardly versus hypofractionated IMRT	300	Completed	Fox Chase Cancer Centre; NCI, USA	NCT 00062309
A phase III randomised study of high-dose 3DCRT/IMRT versus standard dose 3DCRT/IMRT in patients treated for localised prostate cancer	Phase III RCT of dose escalation, stratified for use of IMRT	1520	Active, not recruiting	RTOG; NCI, USA	NCT 00033631
Radiation therapy with or without bicalutamide and goserelin in treating patients with prostate cancer	Phase III RCT of high-dose IMRT versus standard dose IMRT with androgen deprivation therapy	400	Active, not recruiting	Memorial Sloan-Kettering Cancer Center; NCI, USA	NCT 00067015
3D conformal radiation vs helical tomotherapy in prostate cancer	Phase III RCT of 3DCRT versus IMRT	Not stated	Recruiting	Ottawa Health Research Institute, Canada	NCT 00326638
A phase III intensity-modulated radiotherapy dose escalation for prostate cancer using hypofractionation	Phase III RCT of standard IMRT versus hypofractionated, dose-escalated IMRT	225	Recruiting	M.D. Anderson Cancer Center, USA	NCT 00667888
Intensity-modulated radiation therapy with or without decreased radiation dose to erectile tissue in treating patients with stage II prostate cancer	Phase III RCT of IMRT with or without erectile tissue avoidance	200	Recruiting	Fox Chase Cancer Center, USA	NCT 00084552
Intensity-modulated radiation therapy versus permanent interstitial radiation therapy for prostate cancer	Phase II RCT of IMRT versus brachytherapy	50	Recruiting	British Columbia Cancer Agency, Canada	NCT 00407875
A randomised phase III multi-centre trial of conventional or hypofractionated high dose intensity-modulated radiotherapy for prostate cancer (CHHiP)	Phase III RCT of standardly versus hypofractionated IMRT	3163	Recruiting	Institute of Cancer Research, UK	ISRCTN 97182923
Phase III study of hypofractionated radiotherapy of intermediate risk localised prostate cancer	Phase III RCT of standardly versus hypofractionated IGRT delivered with 3DCRT or IMRT	592	Recruiting	Umea, Sweden	ISRCTN 45905321
Randomised trial of external beam radiation with or without short-course hormonal therapy in intermediate risk prostate cancer patients	Phase III RCT of radiotherapy with or without hormonal therapy, delivered with dose-escalated IMRT, 3DCRT or proton therapy	340	Recruiting	M.D. Anderson Cancer Center, Houston, USA	NCT 00388804
Radiation therapy in treating patients with stage II prostate cancer	Phase III RCT of standardly versus hypofractionated radiotherapy, stratified for use of IMRT	1067	Recruiting	RTOG, USA	NCT 00331773

RCT, randomised controlled trial; 3DCRT, three-dimensional conformal radiotherapy; RTOG, Radiation Therapy Oncology Group; NCI, National Cancer Institute; IGRT, image-guided radiotherapy.

in oro- or hypo-pharyngeal cancer patients that has only been published as an abstract (94 patients) and 27 non-randomised comparative studies (1119 patients). There were six other unpublished, ongoing or planned trials in head and neck cancer involving IMRT (Table 1).

Nasopharyngeal cancer (seven studies, two randomised controlled trials)

Pow *et al.* [29] reported on 51 patients with stage II nasopharyngeal carcinoma treated with 2DRT or inverse-planned IMRT. The primary end point was a change in the stimulated whole saliva flow rate. The mean stimulated

whole saliva flow rate and the stimulated parotid flow rate were significantly higher and recovered faster after IMRT than after 2DRT at 8 weeks, 6 months and 12 months. Health-related quality of life (HRQOL) was assessed with the SF-36, European Organization for Research and Treatment of Cancer (EORTC) core and EORTC-H&N35 questionnaires; IMRT significantly improved acute xerostomia-related HRQOL and some measures of physical functionality. However, overall HRQOL recovery was similar in both arms.

Kam *et al.* [25] reported on 60 patients with stage I—II nasopharyngeal carcinoma with 2DRT or inverse-planned IMRT. The primary end point was Radiation Therapy

Table 3
Ongoing, unreported and planned clinical trials in intensity-modulated radiotherapy (IMRT) in breast cancer.

Study name	Principle research question	Number of patients	Status	Trial sponsor	Code
A clinical trial to reduce skin burn induced by breast radiotherapy using intensity-modulated radiation therapy	Phase III RCT of 2DRT versus IMRT	340	Completed	Sunnybrook Health Centre, Canada	NCT 00187343
Prospective randomised clinical trial testing 5.7 Gy and 6.0 Gy fractions of whole breast radiotherapy in terms of late normal tissue responses and tumour control (FAST)	Phase III RCT of standardly versus hypofractionated IMRT	900	Completed	Institute of Cancer Research, UK	ISRCTN 62488883
A randomised phase II trial comparison of radiation therapy techniques in the management of node-positive breast cancer	Phase I/II RCT of 2DRT versus IMRT	Not stated	Recruiting	University of Michigan Cancer Center, USA	NCT 00581256
Randomised trial testing intensity-modulated radiotherapy and partial organ radiotherapy following breast conservation surgery for early breast cancer (IMPORT LOW)	Phase III RCT of standard radiotherapy versus partial breast IMRT	1935	Recruiting	Institute of Cancer Research, UK	ISRCTN 12852634
Randomised trial testing dose escalated intensity-modulated radiotherapy in women with higher than average local tumour recurrence risk after breast conservation therapy for early breast cancer (IMPORT HIGH)	Phase III RCT of standard IMRT versus concomitantly boosted ± dose-escalation IMRT	840	In set-up	Institute of Cancer Research, UK	ISRCTN 4743744

RCT, randomised controlled trial; 2DRT, two-dimensional radiotherapy.

Oncology Group (RTOG)/EORTC grade 2–4 xerostomia at 1 year after radiotherapy. There was a lower mean parotid dose in the IMRT arm and a significantly reduced clinician-assessed grade 2–4 xerostomia with IMRT at 6 weeks and 12 months. The stimulated parotid flow rate was significantly higher after IMRT compared with 2DRT at 6 weeks, 6 months and 12 months and the stimulated whole saliva flow rate was significantly higher at 12 months. There was no significant difference in patient-reported outcomes at any time point, using RTOG/EORTC scores.

Five non-randomised studies have shown that there is no difference in tumour control outcomes between 185 patients treated with 2DRT, 128 with 3DCRT or 219 with inverse-planned IMRT for nasopharyngeal cancer (including

Table 4
Ongoing, unreported and planned clinical trials in intensity-modulated radiotherapy (IMRT) in other tumour sites.

Study name	Principle research question	Number of patients	Status	Trial sponsor	Code
A prospective randomised trial of preoperative IMRT + surgery versus surgery alone for primary retroperitoneal sarcoma	Phase III RCT of preoperative IMRT versus no radiotherapy	Not stated	Completed	Memorial Sloan Kettering Canscer Center; NCI, USA	NCT 00131898
A trial comparing intensity-modulated radiation therapy with conventional radiation therapy in stage IIB carcinoma cervix	Phase III RCT of 3DCRT versus IMRT, both with concurrent cisplatin	Not stated	Recruiting	Tata Memorial Hospital, India	NCT 00193804
Three-dimensional conformal radiation therapy versus intensity-modulated radiation therapy in NSCLC	Phase II RCT of image guided adaptive radiotherapy with 3DCRT versus IMRT	168	Recruiting	M.D. Anderson Cancer Center, USA	NCT 00520702
Three different radiation therapy regimens in treating patients with limited-stage small cell lung cancer receiving cisplatin and etoposide	Phase II RCT of different fractionation regimens, stratified for use of IMRT	Not stated	Recruiting	CALGB; RTOG; NCI, USA	NCT 00632853

RCT, randomised controlled trial; 3DCRT, three-dimensional conformal radiotherapy; NCI, National Cancer Institute; CALGB, Cancer and Leukemia Group B; RTOG, Radiation Therapy Oncology Group.

36 children)[30–34]. Reduced acute toxicity [30], improved stimulated parotid flow rate at 6–12 months [32], improved short-term HRQOL [34] and acceptable late toxicity rates [31] were reported with inverse-planned IMRT.

Oral cavity, laryngeal and oro-/hypo-pharyngeal cancers (16 studies, one randomised controlled trial)

The results of PARSPORT, a UK randomised phase III trial comparing the rate of grade 3/4 xerostomia in 94 patients treated with inverse-planned IMRT with conventional radiotherapy for cancers of the oropharynx and hypopharynx were presented in 2009 [9]. The primary end point was incidence of LENT-SOMA grade ≥ 2 xerostomia 1 year after treatment. Grade ≥ 2 xerostomia was recorded in 74% of patients in the conventional radiotherapy arm and 40% in the inverse-planned IMRT arm at 12 months ($P = 0.005$) and was reduced from 71% to 29% at 18 months ($P = 0.004$). There were no differences in overall survival or locoregional control rates between the groups.

Fifteen non-randomised studies, including four matched analyses, have compared the outcome of patients treated with parotid-sparing inverse-planned IMRT (959 patients) or 2DRT/3DCRT (1455 patients) with predominantly oral cavity, oropharyngeal, laryngeal or hypopharygeal cancers [35–49]. The beneficial effects of inverse-planned IMRT are demonstrated with remarkable consistency, supporting and extending the results from the RCTs: acute [35,47] and late (at least 6 months after radiotherapy) xerostomia was reduced [36,40,43,47], leading to improved xerostomia-HRQOL [37–39,42,47], with increased benefits for inverse-planned IMRT as follow-up increased beyond 12 months [39]. Global head and neck HRQOL [39,47,48] and domains assessing pain [39], communication [46], emotion [39] and eating [46,48] were also improved in the inverse-planned IMRT cohorts. One study also reported a reduced need for long-term percutaneous endoscopic gastrostomy feeding [40]. Two studies have shown a statistically significant improvement in tumour control end points [36,44], whereas four have not [40,43,45,49]; Rothschild *et al.* [44] reported improved 1- and 2-year overall survival with inverse-planned IMRT using positron emission tomography for target volume delineation compared with 3CRT without positron emission tomography (97 and 91% versus 74 and 54%; $P = 0.002$) and Chao *et al.* [36] reported improved 2-year disease-free survival and overall survival with inverse-planned IMRT compared with 2DRT in both the postoperative and definitive radiotherapy setting for oropharyngeal cancer (all $P < 0.01$).

Miscellaneous (five studies, no randomised controlled trials)

Three non-randomised studies have shown that there is no difference in the local control, overall survival or disease-free survival between 110 patients treated with 2DRT, 74 with 3DCRT or 92 with inverse-planned IMRT for sinonasal tumours [50–52]. Chen *et al.* [51] reported a lower rate of late grade ≥ 3 ocular and auditory toxicity with IMRT (both $P = 0.01$), although the rates of severe toxicity were also correlated with decade of treatment. Only two of the 92 patients treated with IMRT developed ≥ 3 grade

complications, with no radiation-induced blindness, whereas four patients developed radiation-induced blindness in the non-IMRT cohorts [50–52]. The Memorial Sloan Kettering Cancer Center report of re-irradiation for recurrent head and neck cancer in 105 patients has shown improved 2-year local control rates with inverse-planned IMRT compared with non-IMRT (52% versus 20%; $P < 0.001$), and that those with local control had better 2-year overall survival [53]. Madani *et al.* [54] compared the outcome of 19 patients treated with inverse-planned IMRT for cervical node metastases of unknown primary with 23 patients treated with conventional radiotherapy. Reduced rates of grade 3 acute dysphagia, xerostomia at 6 months, late dysphagia and/or skin fibrosis were seen in the IMRT cohorts (all $P < 0.03$) although tumour control outcomes were not significantly different.

Prostate Cancer (26 Studies, No Randomised Controlled Trials)

External beam radiotherapy is used in the radical management of many patients with localised and locally advanced prostate cancer. The critical normal structures are the rectum, bladder, femoral head and urethral bulb and during pelvic nodal irradiation, the bowel. As the cure rates from the various therapeutic modalities for localised prostate cancer have been considered to be broadly equivalent [55] and the vast majority of irradiated patients will live beyond 5 years, late toxicity and long-term HRQOL are of paramount importance. There is established evidence for a dose–volume relationship for the development of late rectal toxicity, which at conventional doses is the dominant dose-limiting toxicity. This has been the subject of a recent systematic review, results of which are only summarised here [56]. Dosimetric cut-offs associated with an increased rate of late rectal toxicity are consistent across studies and have been found at 40, 50, 60, 65, 70 and 75–78 Gy. Four studies reported a V_{50Gy} cut-off (percentage volume of rectum receiving 50 Gy) of between <55 and <68%, five a V_{60Gy} cut-off of between <40 and <59%; six a V_{70Gy} cut-off of <25% and five a $V_{75–78Gy}$ cut-off of between <5 and <15%. The clinical variables associated with an increased risk of late rectal bleeding were development of acute toxicity, diabetes, use of androgen deprivation therapy and previous surgery.

Dose escalation to 74–81 Gy has been shown to improve tumour-related outcome in several RCTs [57–61], but survival data are immature and no RCTs exploring dose escalation beyond 81 Gy have been reported. The dose escalation trials have shown an approximate doubling of late rectal toxicity in the higher dose arms and one can expect normal tissue toxicity to increase if further dose escalation is attempted, unless modifications to treatment techniques are made. The effect of internal organ motion caused by changing rectal volume during treatment is now thought to have a clinically significant effect on tumour control, even with the use of IGRT, and the effect may be more pronounced if highly conformal treatment plans are being delivered [62–64]. There is an enormous interest in altered fractionation and this is being evaluated in several ongoing RCTs, such as the CHHiP trial (ISRCTN 97182923) [65].

Inverse-planned IMRT has been shown to achieve dosimetric sparing of the rectum and the penile bulb during prostate $\pm$ seminal vesicle radiotherapy and also of the bowel and bladder during prostate and pelvic nodal radiotherapy (PPN-IMRT) [66–70]. There is a great deal of international clinical experience with IMRT for localised prostate cancer, with series from the USA being reported a decade ago [71]. There are several reports on the use of PPN-IMRT [72,73] and a recent consensus document from the RTOG on outlining for PPN-IMRT for patients with locally advanced prostate cancer [74]. Twenty-six comparative studies were identified (19 full papers and nine abstracts) [69,71,75–98]; 19 were from eight centres in the USA, five from European centres and two from Japan; there have been no published RCTs. Eleven unpublished or ongoing trials were identified (Table 2); these include five dose fractionation trials that will recruit a combined total of over 4000 patients.

The patients were treated with different treatment techniques in both the IMRT and comparative series, including variations in volume, total dose, dose per fraction, margins, IGRT and the use of systemic therapies or previous prostatectomy. Most studies compared acute (17 studies) and/or late toxicity (17 studies), three compared HRQOL and five biochemical control; different end point definitions were used across studies. Acute toxicity end points will not be discussed in detail in this review, although we recognise that there is an association between the development of acute and late genitourinary and gastrointestinal toxicity [56]. In 10 studies the same biological dose was used and in 13 the IMRT patients received a higher dose. Seventeen studies compared outcome of prostate radiotherapy, five of pelvic radiotherapy, one of 3DCRT to the prostate with PPN-IMRT and three compared IMRT with brachytherapy.

Tumour control

The five studies of external beam radiotherapy that have reported biochemical control outcomes have shown no difference between IMRT and 3DCRT, apart from the study by Vora *et al.* [75] in which the IMRT patients received a median dose of 75.6 Gy compared with a median dose of 68.4 Gy in the 3DCRT cohort [75–79].

Late toxicity

Fourteen studies have reported the late toxicity of 2357 patients treated with IMRT and 3682 patients with 3DCRT, eight with the RTOG toxicity scoring system and three the National Cancer Institute Common Toxicity Criteria for Adverse Events. Seven reported a statistically significant reduction in the incidence of late gastrointestinal toxicity [76,80–85] and seven no significant difference [69,75,78,79,86–88], four of each reported higher median doses or larger volumes irradiated in the IMRT series. The median incidence of grade ≥ 2 gastrointestinal toxicity for the IMRT cohorts was 6% (range 0–24%) and for 3DCRT was 15% (range 9–37%). Only one study reported a statistically significant difference in late genitourinary toxicity between its IMRT and 3DCRT cohorts: Zelefsky *et al.* [81] reported a 20% incidence of grade ≥ 2 toxicity at 10 years in an IMRT cohort treated to 81 Gy compared with 12% in the 3DCRT patients treated to 66–75.6 Gy. The median incidence of grade ≥ 2 genitourinary toxicity for the IMRT cohorts in all studies was 18% (range 0–43%) and for 3DCRT was 21% (range 1–45%).

Health-related quality of life

Three studies have reported the changes in HRQOL of 183 patients treated with IMRT to a median dose of 76 Gy and 272 patients treated with conventional radiotherapy or 3DCRT to 70–73.5 Gy at several time points before, during and up to 24 months after radiotherapy [89–91]. Only one study, which included the 30 patients treated without 3DCRT in the comparator group, reported differences in HRQOL between groups and this showed improved bowel HRQOL scores at 3 and 6 months after treatment in the IMRT group [89]. Sexual function was also improved in patients treated with IMRT in two studies [76,89].

Brachytherapy

Two studies published only as abstracts have reported the outcome of iodine-125 low dose rate brachytherapy (LDR) with IMRT [92,93]. Zelefsky *et al.* [92] reported improved 7-year prostate-specific antigen (PSA) relapse-free survival with 144 Gy LDR compared with 81 Gy IMRT in low-risk patients (98% LDR versus 88% IMRT, $P < 0.001$), but not in intermediate patients (93% LDR versus 74% IMRT, $P = 0.08$). Eade *et al.* [93] reported equivalent 4-year PSA relapse-free survival with 145 Gy LDR compared with 74–78 Gy IMRT (93.5% LDR versus 99.5%, IMRT, $P = 0.09$). Significantly increased late grade ≥ 2 genitourinary toxicity with LDR was reported in both studies and in the Eade study for gastrointestinal toxicity. Improved PSA control at 5 years in intermediate risk patients was reported in an abstract comparing a combination of high dose brachytherapy and IMRT (HDR) with ultra-high IMRT to 86.4 Gy alone (98% HDR versus 84% IMRT, $P < 0.001$) [94].

Breast Cancer (Six Studies, Two Randomised Controlled Trials)

Six studies comparing the results of IMRT with 2DRT for postoperative tangential breast radiotherapy were identified for this review. These included two RCTs (664 patients) and four non-randomised comparative studies (875 patients). A third RCT involving 1145 patients comparing 2DRT and forward-planned IMRT in patients with inhomogenous dosimetry has completed and reported its dosimetric results; clinical results are expected in 2010 [21]. There were five other unpublished, ongoing or planned trials in breast cancer involving IMRT (Table 3) and there will be at least 1379 patients included in studies directly comparing the outcome of IMRT versus 2DRT. The dosimetric aim in using forward-planned IMRT for breast cancer is to reduce the volume of tissue receiving <95% or >105–107% of the prescribed dose and could thus be considered to be little more than three-dimensional radiotherapy.

Donovan *et al.* [19] reported on 306 women with stage I–IIIa breast cancer randomised to 2DRT with wedge compensation or forward-planned IMRT delivered with physical compensators or filler beams. All women were

planned to receive 50 Gy in 25 fractions with a 10 Gy tumour bed boost. There was improved breast dosimetry in the forward-planned IMRT arm. The primary end point was a change in breast appearance scored from serial photographs at 1, 2 and 5 years, and 240 patients were available for analysis at 5 years. A change in breast appearance was identified in 58% allocated 2DRT compared with only 40% patients allocated forward-planned IMRT and patients in the 2DRT arm were 1.7 times more likely to have a change in breast appearance than the forward-planned IMRT arm patients (95% confidence interval 1.2–2.5, $P = 0.008$). No significant differences between treatment groups were found in patient-reported breast discomfort, breast hardness or HRQOL. Interestingly, there was a statistically significant difference in the distribution of late changes between the presence or absence of doses >105%, even after adjustment for treatment arm, with an odds ratio of 2.6, which suggests further improvements are possible with improved dosimetry. There was no significant difference in any of the self-assessed parameters, using the EORTC core C-30 and EORTC BR-23 patient self-assessment questionnaires.

Pignol et al. [99] reported on 358 women with early stage breast cancer randomised to 2DRT with wedge compensation or forward-planned or inverse-planned IMRT, both delivered with multiple segments from each gantry angle. All women were planned to receive 50 Gy in 25 fractions with a 16 Gy tumour bed boost if needed. The primary end point was acute radiation-induced toxicity. There was improved breast dosimetry in the IMRT arm. There was reduced acute moist desquamation in the IMRT arm (31% versus 48%; $P = 0.002$). Small breast size and use of IMRT were associated with acute toxicity on multivariate analysis. There was no difference in pain scores or HRQOL, using the EORTC core C-30 and EORTC BR-23 questionnaires, although the timing of this assessment did not tally with maximal acute moist desquamation, which was significantly correlated with pain ($P = 0.002$) and reduced HRQOL ($P = 0.003$).

Three non-randomised comparative studies have reported improved acute toxicity with IMRT delivered with multiple segments from each gantry angle. Freedman et al. [100] reported that there was a reduced rate of moist desquamation with IMRT in a historical matched-pair analysis of 131 patients treated with inverse-planned IMRT (73 patients) or 2DRT (60 patients). Harsolia et al. [101] reported the results of a comparison of 172 treated with 2DRT (79 historical patients) or forward-planned IMRT (93 patients). The patients treated with IMRT had a statistically reduced rate of acute grade 2 toxicity and late grade ≥ 2 breast oedema, but equivalent cosmesis; the benefits of IMRT were larger in women with larger breasts. McDonald et al. [102] reported the outcomes of 240 women treated with either 2DRT or forward-planned IMRT. There was a significantly reduced rate of RTOG grade 2 or 3 dermatitis in the women treated with forward-planned IMRT (39% versus 52%; $P = 0.047$). At a median follow-up of 6.3 years (forward-planned IMRT) and 7.5 years (2DRT), there was equivalent late toxicity, freedom from ipsilateral breast tumour recurrence and overall survival. The fourth report (332 patients) compared the results from two prospective single-arm I/II trials of forward-planned IMRT with a historical control group treated with 3DCRT [103]. The three cohorts of patients were treated with different techniques (3DRT and forward-planned IMRT), overall treatment time, total dose and dose per fraction. The control group received 50.4 Gy to the whole breast with a 10 Gy sequential electron boost to the tumour bed delivered in 32 fractions over 6.6 weeks; one trial group (MARA-1) received 40.4 Gy to the whole breast with a 4 Gy concomitant boost to the tumour bed delivered in 16 fractions over 3.2 weeks and the other trial group (MARA-2) received 50 Gy to the whole breast with a 10 Gy concomitant boost to the tumour bed delivered in 50 fractions over 5 weeks. The phase I/II trials were powered for late toxicity, yet to date, only acute toxicity results have been published. There was a lower rate of acute grade 2 skin toxicity in MARA-1 compared with the other groups, but there was an imbalance in disease stage and a lower use of adjuvant chemotherapy in MARA-1; as acute toxicity was also associated with use of anthracycline- and taxane-based chemotherapy on multivariate analysis, the potential benefit of IMRT *per se* cannot be separated from the other confounding factors.

Endometrial and Cervical Cancer (Four Studies, No Randomised Controlled Trials)

Radiotherapy is used as both primary therapy and in the postoperative setting for cervical cancer, often with concurrent cisplatin; in endometrial cancer, radiotherapy is used primarily postoperatively, although the use may change following recent RCTs [104]. As with nodal irradiation in prostate cancer, the critical normal structures are the rectum, bladder and bowel; IMRT is able to achieve dosimetric sparing of them and in addition bone marrow function can be spared [105,106]. Biological imaging with positron emission tomography is of considerable interest in cervical cancer and can be used to define volumes for focal boosts that can be delivered with IMRT [107]. There are two published guidelines on outlining for gynaecological IMRT [108,109]. Four comparative studies were identified, but these have come from only two research groups reporting serial analyses on their patients. One ongoing trial was identified (Table 4) and a single-arm trial incorporating dose escalation, simultaneous pelvic nodal boosting and concurrent cisplatin for cervix cancer, funded by Cancer Research UK, is due to start recruiting in three UK centres shortly (M. Powell, personal communication).

The University of Chicago group have published three comparative and several non-comparative papers on different aspects of inverse-planned IMRT for endometrial and cervical cancer. Their control population differs from the inverse-planned IMRT group with respect to the proportion of cancer type, previous surgery and use of concurrent chemotherapy. Reduced rates of acute haematological and gastrointestinal toxicity have been reported [110,111]. They published a study in 2003 in which they compared the late toxicity of 36 women treated with inverse-planned IMRT with a contemporaneous cohort of 30 women treated with conventional whole pelvic

radiotherapy. Inverse-planned IMRT women had a shorter median follow-up (20 versus 30 months) and a higher frequency of previous surgery (75% versus 54%). The women treated with inverse-planned IMRT had a lower rate of chronic gastrointestinal toxicity (11% versus 50%; odds ratio 0.16; 95% confidence interval $= 0.04–0.67$) [112].

A Taiwanese group have published a comparative report on 68 patients with cervical cancer who received post-hysterectomy adjuvant chemoradiation. Thirty-three women received inverse-planned IMRT and their outcome was compared with a historical group of 35 women treated with conventional radiotherapy [113]. There were equivalent 1-year locoregional control rates. The IMRT group had reduced acute genitourinary and gastrointestinal toxicity. They also experienced lower rates of late toxicity (gastrointestinal: 6% versus 34%, $P = 0.002$; genitourinary: 9% versus 23%, $P = 0.231$).

Central Nervous System Tumours (Three Studies, No Randomised Controlled Trials)

There are many clinical indications for radiotherapy within neuro-oncology, including several paediatric indications, and there are many critical normal structures, which limit tumour dose (including the brain, brainstem, spinal cord, optic apparatus, cochlear and pituitary). The risk of second malignancies possibly increasing with IMRT is of particular concern in the paediatric setting and proton therapy is increasingly considered the preferred therapeutic modality [114]. Three comparative series that reported the outcomes of 153 patients with glioblastome multiforme, anaplastic astrocytoma or paediatric medulloblastoma were identified. There was no improvement in tumour control in patients with glioblastome multiforme receiving IMRT only (30 patients) compared with those receiving an IMRT boost after initial 3DCRT (12 patients) [115]. Hypofractionated, dose-escalated IMRT for anaplastic astrocytoma (25 patients) was compared with a historical control group treated with non-IMRT (60 patients); there was a significantly better 1- and 2-year local control rate, progression-free survival and overall survival in the IMRT cohort [116]. IMRT has been reported to reduce ototoxicity in 26 children with medulloblastoma treated with radiotherapy and concurrent cisplatin [117].

Anal Cancer (One Study, No Randomised Controlled Trials)

Chemoradiation is standard practice in anal cancer. The conventional radiation technique involves treating the lower pelvic lymph nodes with a boost to the primary tumour and involved nodes, but it results in large dose inhomogeneities. IMRT has been shown to reduce the amount of dose inhomogeneity and can also reduce bone marrow irradiation [118]. One comparative study of 59 patients with anal cancer receiving chemoradiation was identified. The IMRT cohort had less acute diarrhoea and skin/mucosal toxicity, with less unplanned treatment delays [119]. Outlining guidelines have been developed by the RTOG [120].

Lung Cancer (One Study, No Randomised Controlled Trials)

Radiotherapy is used for many patients with both small cell and non-small cell lung cancer, but long-term outcomes remain relatively poor. There are many critical normal structures in close proximity to targets (including the oesophagus, lung, spinal cord and heart if mediastinal nodes are irradiated) and there is evidence for a dose–volume relationship for late pulmonary toxicity [121]. Internal organ motion is of considerable importance and consideration of respiratory motion is critical during target volume delineation, margin application and treatment delivery. One comparative study of 290 patients with non-small cell lung cancer was identified. It compared the incidence of grade ≥ 3 radiation pneumonitis at 12 months in patients receiving concurrent chemoradiation with either IMRT (68 patients) or 3DCRT (222 patients). Both groups received the same mean dose of 63 Gy. IMRT patients had larger PTV volumes, but lower volumes of lung irradiated to 20 Gy (and reduced $V_{15}–V_{65}$) and a lower incidence of grade 3 pneumonitis (8% versus 32%; $P = 0.002$) [122]. Two ongoing trials were identified (Table 4).

Discussion

This review has identified a further three RCTs and 22 non-randomised comparative studies that have been published in the 23 months since the search conducted by Veldeman *et al.* [1], which indicates the high level of interest and research into IMRT currently within the international community. Veldeman *et al.* [1] concluded that the RCT had confirmed the ability of IMRT to reduce the toxicities of radiotherapy compared with non-IMRT, but that the potential for improved HRQOL, tumour control and survival end points suggested by the non-randomised comparisons had not yet been addressed; these conclusions are supported by the results from the additional comparative studies. At this point the total number of patients within published RCTs is only 869 (205 if the breast forward-planned IMRT trials are excluded), although there are another 27 IMRT-related RCTs ongoing and the total number of patients will exceed 13,000.

The primary end points of the six RCTs are all acute (toxicity or salivary flow rates) or late (breast cosmesis or xerostomia) normal tissue effects and in each trial the patients in the IMRT arm have had improved outcomes in these areas. HRQOL has only been shown to be improved with IMRT in one study (acute xerostomia in Pow *et al.* [29]). The trials were not powered to detect differences in HRQOL or tumour control end points, which may explain why the improvements in HRQOL reported in the non-randomised studies have not been seen in the randomised trials. One would expect benefits to HRQOL to be less that benefits to radiation-induced toxicity, and results from the larger ongoing trials will be needed.

The non-randomised studies in head and neck cancer consistently show that IMRT can be used to reduce the dose to at least one parotid, preserving parotid function and

reducing late xerostomia and improving HRQOL. Significantly improved tumour control and survival has been reported in three of the studies [36,44,53]; further improvements may be seen if the radiation dose can be escalated with IMRT, as suggested by the phase I study from the Royal Marsden Hospital presented at ESTRO 27 [123] and being studied in one ongoing trial. There have been reports of marginal and edge-of-volume recurrences with IMRT, including within spared retropharyngeal and parotid nodes [4,124,125], but reports from larger centres are generally reassuring, with most failures being within the high dose region [126–128].

The results of the non-randomised studies of IMRT for prostate cancer are similarly convincing. The median rate of late rectal toxicity was 6% in the IMRT cohorts and 15% in the 3DCRT cohorts, despite the IMRT patients often receiving higher median doses and/or treatment to larger volumes. There seems to be little effect on genitourinary toxicity, although increased rates at very high doses with IMRT are concerning [81], and there are relatively few HRQOL data. The reduced rectal irradiation achievable with IMRT does not seem to adversely affect PSA control and is being used to safely deliver dose-escalated radiotherapy, as escalation with 3DCRT to 74 to 78 Gy approximately doubles the rate of late moderate to severe rectal toxicity [129], and hypofractionated treatment [130]; this is the focus of five of the 11 ongoing trials.

Cost-effectiveness modelling for IMRT in prostate cancer has been conducted by the Institute of Clinical and Economic Review in the USA. They carried out an analysis assuming IMRT reduced the incidence of late rectal toxicity from about 14% to 4%, with each case costing $313 000 to manage, and that the cost per course was $42 450 compared with $10 900 for 3DCRT. They assigned a net health benefit rating of 'incremental', denoting a small health benefit and judged the comparative value of IMRT as 'low' on the basis of high incremental cost-effectiveness ratio and the high cost of preventing a single case of proctitis ($117 000 for patients with a prior probability of proctitis >75%). Equivalent tariffs have not yet been set within the National Health Service, but one centre has costed 3DCRT and IMRT for head and neck cancer at £10 900 and £12 800, respectively (N. Close, personal communication). Using these values in the Institute of Clinical and Economic Review model results in a £16 654 cost of avoiding each case of proctitis, which is just over 5% of the US estimated costs and, if accurate, would have a dramatic effect on the resulting conclusions. Formal cost-effectiveness modelling within the UK is a priority.

The comparative studies in breast cancer report improved toxicity and long-term cosmesis, but no improvement in HRQOL for forward-planned IMRT compared with conventional tangential breast 2DRT. These studies have been included within this review although forward-planned IMRT for breast cancer does not meet many of the International Atomic Energy Agency's criteria for IMRT [11] as it is clearly distinct as a technique from the conventional treatments and as it has been the subject of several RCTs. Forward-planned IMRT planning techniques have been used in other clinical situations, often before the term IMRT was in regular use, and this review has not attempted to included these in this report.

There have been several non-randomised comparative studies in other tumour sites; they have shown that the normal tissue avoidance or reduced hot spots within normal tissue, both achievable with IMRT, reduce the incidence of radiation-induced toxicity. Such results have been found for gynaecological cancers, anal cancer, non-small cell lung cancer and childhood medulloblastoma and four trials are completed-unpublished or ongoing in this area. But to what extent should we wait for results from randomised trials before accepting that IMRT is a superior treatment in less common clinical situations? In drawing conclusions on the appropriate use of IMRT within the UK, one must be cautious of over-interpreting results from such studies, particularly if a historical control group has been used, as there are many sources of clinical and publication bias and several studies have shown improved outcome over the decades [51,131]. On the other hand, there is an ongoing debate over the potential for over-reliance on randomised trials and this may have particular relevance for the assessment of new technologies and rare clinical scenarios. In his Harvian oration of 2008, Professor Rawlins discussed the relative merits of the randomised trial and quoted Bradford Hill, who was instrumental in their development, 'any belief that the controlled trial is the only way would mean not that the pendulum had swung too far but that it had come right off the hook' [132]. Although some ongoing trials are still comparing IMRT with non-IMRT, most are using IMRT to address other issues, such as fractionation or dose escalation, and we support this approach.

The UK has the infrastructure to conduct large multi-centre trials, but this is less true for technical radiotherapy, as there are still significant hurdles restricting the introduction of IMRT into the UK [133]. Steps to address this nationally have been taken [134] and then we will be in an excellent position to design and run trials to address our priority issues [135]. One particular strength in the UK is the extensive support available from the National Cancer Research Institute Radiotherapy Trials Quality Assurance Group [136].

Conclusions

This study has identified 61 comparative studies of IMRT and non-IMRT. The six RCTs in breast and locally advanced head and neck cancers have all shown a significant improvement in their normal tissue-focused primary end points. The non-randomised studies show highly consistent sparing of acute and late radiation-induced side-effects across multiple tumour sites and this should be considered sufficient to implement IMRT across the UK. There will be over 13 000 patients within ongoing IMRT-related studies and the UK will be well placed to design and run highly relevant IMRT clinical trials once IMRT is implemented nationally.

Acknowledgements

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